

## REMARKS

Claims 1-9 are pending.

Claims 4-6 and 8-9 are withdrawn due to a restriction requirement.

The specification is currently amended to incorporate cross reference to related applications.

No new matter is added.

Claims 1-3 and 7 are presented for reconsideration.

### **Restriction Requirement**

Claims 1-9 are subject to restriction as set forth in the Office Action. Responsive thereto, the election of Group I, corresponding to claims 1-3 and 7, is affirmed.

The Applicants respectfully traverse the restriction requirement.

The Examiner raises a lack-of-unity rejection reasoning that claims 1-9 are not linked by a special technical feature defining a contribution over the art.

The Examiner apparently identifies the structural formula of the present fluvastatin monosodium salt as the intended feature of the invention (see office action page 3, 2<sup>nd</sup> paragraph from bottom). As clearly stated on page 1 of the present specification and apparent from the present claims, the special technical feature distinguishing the present subject is represented by the crystalline form G of said fluvastatin monosodium salt. This crystalline form of fluvastatin monosodium salt is characterized by the set of x-ray reflections recited in present claim 1.

Since there is a distinguishing technical feature linking present claims, and the present subject claimed corresponds to the combination (3) on page 4 of the Office Action, i.e. product (claims 1-3) along with its process of manufacture (claims 4-6 and 8-9) and use (claim 7). Therefore, under 37 CFR 1.475(b), the different categories of invention have unity of invention.

Accordingly, the Applicants request that Group I and Group II be rejoined.

### **Claim Rejection – 35 USC 112 Second Paragraph**

Claims 1-3 and 7 are rejected under 35 USC 112 second paragraph as being indefinite for failing to particularly point and distinctly claim the subject matter which applicant regards as the invention. Claims 1-3 and 7 do not contain sufficient physical data that particularly points out and distinctly claims the product that Applicant regards as the invention.

The Examiner discusses some theoretical thoughts on the reliability of powder x-ray diffraction patterns (PXRD) upon which the present invention is based and thus rejects present claims under 35 USC 112 second paragraph.

The Examiner finds support for her rejection in a number of references:

- a) Page 1843 of US Pharmacopia (right hand column, 3<sup>rd</sup> paragraph) generally reminds of careful evaluations to be undertaken,
- b) the occasional occurrence of preferred orientation in PXRD which may suppress peaks, which theoretically should occur (Bernstein, p. 117-118), and may misguide the analyst (Davidovich, p. 16, conclusion),
- c) identical PXRDs for different chemical entities (Bernstein, p. 272), and
- d) small deviations in d-values in case of varying air humidity as noted in US 2003/032666.

While the recommendation of general precautionary measures as given by (a) certainly is always helpful in science, any suppression of peaks due to preferred orientation as noted in (b) is also accompanied by a general reduction of crystal planes available for reflection, and thus detectable since a peak suppressed is not replaced by other close-by peaks (see fig. 4.21 of Bernstein page 118).

It also deserves emphasis that references (b) generally compare experimental data (where preferred orientation may or may not occur) with theoretical PXRDs (no consideration of preferred orientation); while in the present invention experimental data are used which are compared with other experimental data of the same type. In consequence, the PXRD provides a fingerprint which can be used to

distinguish one crystal from another (see, for example, Azaroff et al. The Powder Method (1958), page 11).

The problem mentioned under (c) has no connection with the present experimental work, where the one known educt material is brought in contact with water only, and chemical identity of the material (see office action page 5, lines 2-3 from bottom) has not been in question.

Small deviations in air humidity may result in small deviations of d-values as mentioned in (d); distinguishing features of the present crystal form is discussed further below.

Summarizing the above, the Applicants aver that PXRD is a well recognized method which is ideally suitable for the detection and characterization of polymorphic crystal forms. This appears to be fully accepted by the USPTO, as many patents have been granted on polymorphic forms characterized by that method. The Examiner is directed to the present citations.

The Applicants therefore aver that the 35 USC 112 second paragraph rejections are addressed and overcome.

#### **Claim Rejection – 35 USC 112 First Paragraph**

Claim 7 is rejected under 35 USC 112 first paragraph as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention.

The Examiner rejects present claim 7 as not enabling reasoning that the claim would cover subjects not disclosed; such as compositions no longer containing the present polymorph as a result of, for example, dissolving the present crystalline form or its conversion into another polymorph.

Present claim 7 covers a composition which contains an effective amount of the crystalline polymorphic form G of claim 1. Any composition wherein the original polymorphic form G is converted into another crystalline polymorphic form, or is dissolved, is clearly excluded from present claim 7.

Present claim 7 does not seek coverage for anything outside the present invention.

The Examiner further reasons (page 10, 1<sup>st</sup> paragraph) that the unpredictability of formulating a composition with a specific crystalline structure would put an undue burden on the skilled person wishing to obtain a formulation actually containing the present crystalline form.

Present specification (page 2, 4<sup>th</sup> paragraph) and the Working Example clearly show the conditions of formation and persistence of the present crystalline form G.

Thus, the Applicants aver that the present specification is fully enabling for the skilled worker to formulate a composition containing the present crystalline form G of fluvastatin monosodium salt.

The Applicants therefore aver that the 35 USC 112 first paragraph rejection is addressed and overcome.

#### **Claim Rejections – 35 USC 102(b)**

Claims 1-3 and 7 are rejected under 35 USC 102(b) as being anticipated by Van der Scaaf et al. in WO 2002/36563 (US 6,858,643) and Van der Shaaf et al. in US 2003/0032666 (US 6,696,479).

The instant invention has a priority date of October 16, 2003 according to EP 03103841.7. US 2003/0032666 was published on February 13, 2003. Therefore, the cited art, US 2003/0032666, does not qualify as prior art under 35 USC 102(b).

While the present crystalline forms are made up of the racemic mixture of the (3R,5S) **and** (3S,5R) enantiomer of fluvastatin sodium (see line 8 on present page 1), the cited WO 2002/36563 discloses crystalline forms of enantiomerically pure fluvastatin sodium (containing only one enantiomer, (3R,5S) **or** (3S,5R)).

Since identity of the species making up the crystals is a precondition for identity of any 2 crystals, it is clear that the crystal forms of WO 2002/36563 cannot anticipate the present invention.

A fundamental difference between the instant invention and the compound of WO 2002/36563 is that a racemic mixture rather than the pure enantiomer is used.

In the following, experimental x-ray data of the present form G is compared with experimental x-ray data for polymorphic forms reported in the WO 2002/36563; this is done by comparing the strongest reflection lines (intensity "medium" or higher) since these lines are detected with lowest error (see also U.S. Pharmacopeia #23 page 1844, bottom of right hand column).

The peaks of highest intensity (m or above) of the present form G crystal polymorph [d-values, Å] are:

Form G:        10.1 (m)  
                  7.6 (vs)  
                  6.10 (s)  
                  5.09 (m)  
                  4.37 (s)  
                  3.07 (m)

In order to permit a comparison with a clearly distinguished crystal and thus show the effectiveness of the method, the peaks of highest intensity (m or above) according to WO 2002/36563 [d-values, Å] are listed herein below:

Form E:	7.4 (s)	Form A:	24.2 (m)
	6.9 (m)		8.2 (s)
	6.2 (m)		7.1 (m)
	5.04 (vs)		4.90 (m)
	4.85 (vs)		4.73 (m)
	4.46 (m)		4.08 (m)
	4.09 (s)		
	3.93 (m)		
	3.21 (m)		

Form B1:	8.6 (m)	Form B2:	8.8 (m)
	8.1 (m)		4.96 (s)
	4.93 (s)		4.81 (s)
	4.78 (s)		4.14 (s)
	4.12 (s)		

Form C:	9.3 (m)	Form D:	7.5 (s)
	6.9 (s)		6.0 (m)
	4.97 (vs)		5.01 (s)
	4.75 (s)		4.83 (m)
	4.62 (m)		4.13 (m)
	4.13 (m)		
	4.04 (m)		

A comparison of the characteristic spacings of present form G with those of forms E, A, B1, B2, C, and D of WO 2002/36563 inter alia shows the following:

Form E shows the 2 neighboring very strong reflections for  $d=4.85$  and  $d=5.04$ , while this region shows only 1 medium reflection for  $d=5.09$  in present form G. The 2 reflections of form E belong to the strongest reflections of this crystal form and would occur in the present PXRD of form G, if there is any contamination by form E, or even the alleged identity with that form. This is not the case. Present form G is clearly distinguished from form E.

Similarly, form A shows a strong reflection for  $d=8.2$ , which is absent in present form G. Present form G thus is clearly distinguished from form A.

Form B1 shows a strong reflection for  $d=4.93$ , which does not find any counterpart in present form G. Present form G thus is clearly distinguished from form B1.

Form B2 shows a strong reflection for  $d=4.96$ , which does not find any counterpart in present form G. Present form G thus is clearly distinguished from form B2.

Form C shows a strong and very strong reflections for  $d=6.9$  and  $d=4.97$ , which do not find any counterparts in present form G. Present form G thus is clearly distinguished from form C.

Form D shows a strong reflection for  $d=5.01$  and the medium intensity reflection  $d=4.83$ , which do not find any counterparts in present form G. Present form G thus is clearly distinguished from form D.

The Examiner specifically points out that a number of d-values of prior art form D are correlated within a range of  $0.9 \text{ \AA}$  with present form G. In order to evaluate the Examiner's argument, the d-values of

these 2 forms are collected in the following table; although a deviation of 0.9 would be quite high, reflections within this margin are shown in the same line, where possible:

Number	d-values/Å	Intensity	d-values/Å	Intensity	Deviation/Å
1	29.2	w	30.1	w	+0.9
2	15.0	<b>vw</b>			
3	10.1	m	10.0	w	-0.1
4			8.6	<b>w</b>	
5			8.3	<b>w</b>	
6	7.6	vs	7.5	s	-0.1
7			6.5	<b>w</b>	
8	6.1	s	6.2	<b>vw</b>	+0.1
9			6.0	<b>m</b>	
10	5.09	m	5.01	s	-0.08
11			4.83	<b>m</b>	
12	4.37	s	4.31	w	-0.06
13			4.13	<b>m</b>	
14	3.83	w	3.95	w	+0.12
15			3.54	<b>w</b>	
16			3.44	<b>vw</b>	
17	3.07	m	3.00	w	-0.07

The Examiner lists in the bridging paragraph on pages 12/13 peaks Nos. 1, 3, 6, 8, 10, 12, 14 and 17 of form D, correctly stating that these peaks find their correspondent within a range of 0.9 in the XRPD of present form G.

Translated into angles, a deviation in d-spaces of 0.4 Å (as mentioned in the rejection concerning US 2003/0032666 on page 13 of the Office Action) would correspond to an error in scattering angle  $2\theta$  of about 0.4 degrees for larger d-spacings of about 10 Å, and a huge error of about 1.6 degrees for smaller d-spacings of about 5 Å (following the Bragg-condition:  $2d \sin \theta = \lambda$ ; wavelength 1.54 Å corresponding to copper k- $\alpha$  radiation). A deviation in d-spaces of 0.9 Å would correspond to an even larger error in scattering angle  $2\theta$ .

The error reported by Brittain and quoted by the Examiner (Office Action page 13, lines 8-11) is plus or minus 0.2 degrees which is much smaller than the deviations presently observed; the reference



quoted by Brittain, US Pharmacopeia, even states for the scattering angle  $2\theta$  a reproducibility of not more than plus or minus 0.1 degrees (see page 1844, bottom paragraph of right hand column). This is a clear indication that deviations observed even for “matching” peaks are the result of a deviation of the crystal form rather than error of measurement.

To complete the above comparison of the 2 XRPDs, however, it further needs to be emphasized that 8 peaks for form D lack any correspondent peak for form G (i.e. those marked in boldface in the above table). It further needs emphasis that the intensities of reflections are far away from matching (for example, see peak No. 8: strong reflection in present form G, very weak reflection in form D).

The Examiner’s rejection of present form G as anticipated by prior art form D thus appears to be based on selective reading and hindsight rather than view on the prior art.

Summarizing the above, the Applicants aver that the subject of present invention is novel and is not anticipated in the light of WO 2002/36563.

The Applicants therefore aver that the 35 USC 102(b) rejections are addressed and overcome.

### **Claim Rejections – Double Patenting**

Claims 1-3 and 7 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7 and 20 of US 6,858,643.

Claims 1-3 and 7 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11 and 12 of US 6,696,479.

As explained above, neither US 6,858,643 nor US 6,696,479 teaches or suggests the subject matter as presently claimed. Thus, the filing of any terminal disclaimer appears neither necessary nor appropriate.

The Applicants therefore aver that the nonstatutory obviousness-type double patenting rejection is addressed and overcome.

### **Objections – Content of Specification**

The specification does not incorporate cross reference to related applications. As requested by the Examiner, the specification is currently amended to include a cross reference to related applications.

The Examiner is kindly requested to reconsider and to withdraw the present rejections and objections.

Applicants submit that the present claims are in condition for allowance and respectfully request that they be found allowable.

Respectfully submitted,



for

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Enclosure: Two month extension of time

Azaroff et al., The Powder Method (1958), page 11.